REMARKS

Restriction

Applicants respectfully disagree with the Office Action's assessment that it would pose a serious burden on the Examiner to search at least some of the withdrawn claims. For example, withdrawn claims 22, 23, 28, 29, 31 and 32 are directed to products comprising the compound of allowed claim 1of group I, which claims should readily be also allowed. Products comprising a patentable compound should be readily patentable as well for at least the same reason as the compound was. No further, or only a minimal, search would be necessary to allow these claims.

Furthermore, the products of the above identified claims are combinations of the compound of claim 1 and other components. As such, it is respectfully submitted that the compound of claim 1 and other components are related as subcombination-combination. Since they are related as combination-subcombination, the standard for requiring restriction herein is not met.

> In order to establish that combination and subcombination inventions are distinct, two-way distinctness must be demonstrated. To support a requirement for restriction, both two-way distinctness and reasons for insisting on restriction are necessary , i.e. separate classification, status, or field of search. See MPEP §808.02. If it can be shown that a combination, as claimed
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> (1) does not require the particulars of the subcombination as claimed for patentability (to show novelty and unobviousness), and
>
> (2) the subcombination can be shown to have utility either by itself or in other and different relations, the inventions are distinct. When these factors cannot be shown, such inventions are not distinct.
> (M.P.E.P. §806.05(c))

It is submitted that the first requirement for two-way distinctness is not established herein. The combination does require the particulars of the subcombination. All the products of the above identified claims require the presence of the allowed compound of claim 1. The combination claims are dependent upon the subcombination-compound claims and the subcombination-compounds are an essential distinguishing feature of the combination-compositions.

It is respectfully submitted that when the relationship between the claims are properly characterized, there is no basis for restriction of these claims. Thus, the restriction requirement should be withdrawn over these claims.

The same is true with respect to withdrawn claim 24, which is directed to a method of claim 9 (not withdrawn) and further comprises administering an additional compound. If claim 9 were to be allowed, one administering a further compound in addition to the compound administered in claim 9, would necessarily practice the method of claim 9, which would be allowable on its own. Thus, the method of claim 24 should be also allowable for at least the same reason claim 9 may be. Thus, no further, or maybe only minimal, search would be necessary to readily allow claim 24 once claim 9 would be allowed.

With respect to claim 30, directed to a method of using a composition of claim 29, whose withdrawal should be revoked for the reasons discussed above and allowed, MPEP § 821.04, Rejoinder, states that "if the elected invention is directed to the product and the claims directed to the product are subsequently found patentable, process claims [both process of making and using] which either depend from or include all the limitations of the allowable product will be rejoined." Accordingly, rejoinder of this claim is respectfully requested in accord with the rejoinder provisions of the MPEP.

Reconsideration is respectfully requested.

Compound claim 33 directed to an intermediate is cancelled without prejudice.

Use of Trademarks

The Office Action points out the use of trademarks on page 29 of the specification and notes that such should be capitalized and accompanied by generic terminology. All the trademarks used on page 29 are already capitalized and are already described to refer to products which are conjugated estrogens used in hormone replacement therapy. If applicants missed anything, please point out the same.

Claim Rejections Under 35 USC § 112, first paragraph

The method of use claims are rejected as allegedly not enabled.

With respect to the enablement rejection over the method of treatment claims, first and foremost, a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling

requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971). "The PTO must have adequate support for its challenge to the credibility of applicant's statements of utility". (The quoted statement was made in the context of enablement, i.e., the how-to-use requirement of the first paragraph of section 112.) See also *In re Bundy*, 209 USPQ 48 (1981). The only relevant concern of the Patent Office should be over the truth of assertions relating to enablement. The first paragraph of section 112 requires nothing more than objective enablement. See *In re Marzocchi, supra.*

The Examiner has not established any basis to doubt objective enablement. The Examiner has also provided no support for establishing that one of ordinary skill would doubt the objective truth of the asserted utility, which is enabled by the specification. The enablement rejections by the Examiner are thus unfounded. The rejection therefore was improper under *In re Marzocchi.*

The claims rejected are directed to the treatment of, for example, inhibiting tyrosine kinase, of treating a solid tumor in a mammal, small cell lung carcinoma, pancreatic cancer, diabetic retinopathy, etc., the treatment of which are not objectively doubtable. There is no indication that one of ordinary skill in the art would have questioned the effect of the drugs in view of the disclosure and the state of the art. See *Rasmusson v. Smithkline Beecham Co.*, 04-1191, 04-1192 (Fed. Cir. June 27, 2005).

As discussed above, this is adequate to objectively enable an invention. Without proper reason or evidence to doubt the objective truth of the enabling disclosure, the Examiner improperly required a guarantee and/or evidence to prove utility and/or to support enablement. "Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility." *See In re Bundy*, supra.

Instead of relying on proper probative evidence, the rejection is improperly based on bare allegations. No evidence has been presented which would demonstrate that the guidance provided by the specification is inadequate to enable the preparation and use of the claimed compounds without undue experimentation.

The rejection starts with the premise, allegation, that the "pharmaceutical art is

unpredictable," citing *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) in support. However, there is no basis for such an allegation or conclusion. Fisher does not stand for the proposition that the pharmaceutical art is unpredictable *per se*. The court in *Fisher* stated that "in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." Thus, merely concluding that the pharmaceutical art is unpredictable without looking at the factors involved is an improper basis for the allegation. As discussed in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), used by the Examiner as the basis of the rejections, the court therein teaches that "whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." No factual basis is provided by the Office Action for the conclusion that the relevant art is unpredictable.

Additionally, with respect to *Fisher*, the court held therein that the appellant, who was the first to achieve a potency of greater than 1.0 for adrenocorticotrophic hormones ("ACTHs"), had not enabled the preparation of ACTHs having potencies much greater than 2.3, and the claim recitations of potency of "at least 1" rendered the claims insufficiently supported under the first paragraph of 35 U.S.C. §112. Thus, the situation and question considered by the court in *Fisher* is very different than the one present case. The applicant therein was the "first" to achieve a potency of greater than 1.0, but not greater than 2.3, while the claims were directed with an open end to a potency of "at least 1." In the present case, other compounds are already known to treat conditions claimed, and the claims are not open ended.

The Office Action also alleges right up front that there is no "absolute predictability" in this art. The enablement rejection also ends with the allegation that there is "no assurance of success." These allegations may be correct, but they do not weigh against applicants, but rather against the merits of the rejection. No such "absolute predictability" and/or "assurance of success" is required for an invention to be patentable, especially not in an art where "absolute predictability" and/or "assurance of success" is not even possible with respect to treatment of very well-known and easily curable diseases by medical practitioners. The medical and pharmaceutical fields are not fields full of absolute predictabilities and assurance of success, and the law does not require them to be either.

Instead, The Federal Circuit in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1441 (Fed. Cir. 1995), stated that

> usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Applicants also point to *In re Bundy*, 642 F.2d 430, 209 USPQ 48, (CCPA 1981), where the disclosure only established the basic pharmacology for the compounds, but where no examples were provided. The specification stated that the compounds of the invention possess activity similar to E-type prostaglandins. Nevertheless it was found that sufficient guidelines as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of section 112 is the disclosure of some activity coupled with knowledge as to the use of this activity."

Additionally, the Office Action alleges that in the pharmaceutical arts, due to its unpredictability each embodiment is required to be individually assessed for physiological activity. On page 5 of the Office Action, an exhaustive search requirement is alleged. However, this is not undue experimentation in the field of pharmaceuticals, but rather an industry wide acceptable routine amount of testing. As discussed in *Wands*, the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Here, the compounds are enabled and the rejection only concerns the method of use claims. Applicants provide specific guidance as to how the claimed compounds can be tested for activity levels. See, for example, page 37, line 31 to page 42, line 27 and the pharmacological tests on page 49 of the specification.

While the amount of work may require considerable effort (although not admitted), no undue experimentation is required in determining activity levels. In the pharmaceutical art testing hundreds and thousands of compounds, i.e., screening for activity, is merely routine.

With the current state of the art at the time of filing there is no basis for a rejection for lack of enablement in a case where applicants provide guidance as to how the activity of the

compounds may be tested. At this point it takes merely routine testing/screening, which is not undue experimentation, to determine the activity level of a variety of compounds within the claims.

The Office Action also alleges under the enablement rejection that the "scope" of a number of the methods is "unclear." However, the clarity of the scope of a given term is not a section 112, first paragraph issue. Nevertheless, applicants submit that each of the terms alleged to have unclear scope recited on page 4 of the Office Action is clear to one of ordinary skill in the art. The fact that the terms may encompass a number of specific diseases, does not render these terms unclear.

The Office Action also alleges that it is not seen how the test performed correlates to the various methods of use, e.g., the results of the tested activity and the correlation of tyrosine kinase inhibition to diseases is questioned. Applicants submit that the specification teaches such, and points to a large number of references which demonstrate the nexus between the tests for the activities of the compounds and the claimed methods of uses. For example, the specification teaches that "tyrosine kinases have been shown to be important contributing factors in cell proliferation, carcinogenesis and cell differentiation," (see page 1, lines 26-27); "Both receptor type tyrosine kinases and non-receptor type tyrosine kinases are involved in cellular signalling pathways leading to numerous pathogenic conditions, including cancer, psoriasis and hyperimmune responses," (see page 2, lines 28-31); "various receptor-type tyrosine kinases, and the growth factors binding to them, play a role in angiogenesis, although some may promote angiogenesis indirectly (Mustonen and Alitalo, *J. Cell Biol.* 129:895-898, 1995)." (see page 2, lines 32-34); "the murine version of this receptor has also been called NYK (Oelrichs et al., *Oncogene* 8(1):11-15, 1993). VEGF and KDR are a ligand-receptor pair which plays a vital role in the proliferation of vascular endothelial cells and the formation and sprouting of blood vessels, referred to as vasculogenesis and angiogenesis respectively" (see page 3, lines 3-9); "Solid tumours can therefore be treated with tyrosine inhibitors since these tumours depend on angiogenesis for the formation of the blood vessels that are necessary to support their growth, ...[this is followed by a teaching of specific types of tumors]" (see page 3, lines 25-end of page). Further teachings between tyrosine kinase activity and other activities and claimed methods are taught in the specification on pages 4-13, with many references cited in support.

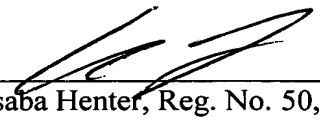
Thus, a nexus between the activity of the compounds and the claimed methods is more than adequately established in the specification and is more than adequately recognized by those of ordinary skill in the art. Thus, the usefulness of a compound that inhibits, for example, tyrosine kinase activity to treat the claimed diseases is not objectively doubtable to a person of ordinary skill in the art.

The Office Action alleges that "treating all forms of 'solid tumor' known to man and yet to be discovered by man is wholly inoperable." This allegation seems to miss the point that treatment of all forms of known and not yet known tumors is not required for enablement. In the present case, studies on the tyrosine kinase pathway, for example, and related diseases are numerous; and thus, one of ordinary skill in the art would know how to proceed in cases where inoperative embodiments may occur, if any. Applicants invented a broad invention, which under the applicable law, does not have to be limited to specific embodiments since the invention is not so limited. See *In re Dinh-Nguyen*, 181 USPQ 46 (CCPA 1974), and *In re Sarett*, 140 USPQ 474 (CCPA 1964).

Applicants provided adequate support and evidence to enable the method claims. Reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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